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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/603,658 06/23/00 ZHU

L 25636-703

021971 HM12/0925
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650 PAGE MILL ROAD
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EXAMINER

PRASTHOFFER, T

ART UNIT

PAPER NUMBER

1627
DATE MAILED:

09/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary <i>file copy</i>	Application No.	Applicant(s)
	09/603,658	ZHU ET AL.
Examiner	Art Unit	
Thomas W Prasthofer	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
 - Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 27 June 2001 .

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-9, 13-19 and 22-44 is/are pending in the application.

4a) Of the above claim(s) 28-34 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-9, 13-29 and 35-44 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). _____
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) Other: _____

Detailed Action

Status of the Application

Receipt is acknowledged of an amendment with a response to an office action on June 27, 2001 in Paper No. 6.

Status of the Claims

Claims 1-38 were pending in the present application. Claims 10-12 and 20-21 were cancelled and new claims 39-44 were added as per applicant's request received June 27, 2001 (paper No. 6). Claims 28-34 were withdrawn from further consideration as being drawn to non-elected inventions in paper No. 5. (Note that there is a typographical error on the office action summary of Paper No.5 which incorrectly lists claims 24-34 as being withdrawn rather than claims 28-34.)

Claims 1-9, 13-19, 22-27, and 35-44 are now pending and being examined on their merits.

Withdrawn Objections and Rejections

1. The objections to claims 25 and 35 in the office action mailed March 20, 2001 (Paper No. 5) are withdrawn in response to applicant's amendments.
2. The rejection of claims 1-27 and 35-38 under 35 U.S.C. 101 and the associated rejection under 35 U.S.C. 112, first paragraph in ¶ 9 of Paper No. 5 are withdrawn in response to applicant's arguments.
3. The rejection of claims 10-13, 20, and 21 under 35 U.S.C. 112, second paragraph are withdrawn in response to applicant's amendments.

4. The rejections of claims 1-21, 25-27, and 35-38 under 35 U.S.C. 102 (b) as being anticipated by Hoeffler et al. and claims 1-3, 15-17, 19-24, 26, 35, and 36 under 35 U.S.C. 102 (b) as being anticipated by Filupa et al. are withdrawn in response to applicant's amendments.

Maintained Rejections

The statutory basis for the following rejections can be found in an earlier office action (Paper No. 5).

Maintained Rejections – 35 U.S.C. 112, first paragraph

6. Claims 1-9, 13-15, 22-27, and 35-38 remain rejected under 35 U.S.C. 112, first paragraph, for reasons made of record in Paper No. 5. Applicant's arguments have been carefully considered and not found to be persuasive because applicant argues only utility in the response received June 27, 2001 (Paper No. 6). Applicant does not address possession of the claimed invention, which is the basis for the rejection in paragraph 10 of Paper No. 5. Accordingly, the rejection is maintained.

New Grounds of Rejection Necessitated by Applicant's Amendment

New Grounds of Rejection – 35 U.S.C. 112, first paragraph

7. Claims 13 and 39-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER).

There is no support in the specification for claim 13 as amended to recite "*library of fusion proteins encode a class of multimeric proteins*" or new claims 39-44. Applicant may overcome this rejection by pointing out where in the specification support can be found for the amendment to claim 13 and new claims 39-44.

In accordance with MPEP 714.02 applicant should specifically point out support for any amendment made to the disclosure.

New Grounds of Rejection – 35 U.S.C. 112, second paragraph

8. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the term “class of multimeric proteins” are not clear. It is not clear if applicant intends the term “class” to mean structural classes and/or functional classes. It is also unclear how one using the invention is to determine the metes and bounds of any particular “class.”

New Grounds of Rejection – 35 U.S.C. 103(a)

9. Claims 1-9, 13-19, 22-27, and 35-44 rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeffler et al. (1999), WO 99/28502, Filupa et al. (1998) WO 98/49198, and Gietz et al. (1995) Methods in Molecular and Cellular Biology 7(3) 254-269.

The Hoeffler et al. reference teaches libraries of yeast expression vectors encoding libraries of single chain antibodies comprising a first nucleotide sequence encoding either V_H or V_L subunit, a second nucleotide sequence encoding either V_L or V_H subunit, and a peptide linker that connects the two subunits (see, for example, page 5, lines 1-16, page 7, lines 10-13, and figure 4). The yeast expression vectors include the yeast 2μ and bacterial origins of replication and are yeast-bacteria shuttle vectors (figure 4). The single chain antibody libraries are comprehensive populations of V_L and V_H subunits (vary independently from one another) linked by short, flexible peptide linkers (page 8, lines 16-17). The reference presents an invention that can probe an animal’s entire repertoire of $> 10^{12}$ combinations of light and heavy variable chains (page 11, lines 12-15, 21-22, and 25). The yeast strains used can be diploid or haploid and may be mated (page 22, lines 21-24). The use of α and α strains of haploid yeast for mating is the most common method of yeast mating. The preferred linker in the Hoeffler et al. reference if a

[(Gly)₄Ser]₃ peptide (page 24, line 27). The source of DNA for generating the single chain antibody expression vectors may be from immunized or non-immunized animals including humans and mice and from tissues including spleen cells and lymphoblastoid cells (page 32, lines 5-10). The immunoglobulin variable regions can be amplified without prior knowledge of their sequences (or binding properties) (page 33, lines 5-6) and the fusions can be tagged with poly-Histidine for purification (page 43, lines 24-25). Vectors encoding activating or DNA binding domains of transcriptional activators are taught on page 5. Transcriptional activators such as GAL4 are taught on page 12.

Hoeffler et al. do not explicitly teach linker sequences that are 30-120, 45-102, or 45-63 bp in length or yeast libraries with a diversity of at least 1x10⁷.

The Filupa et al. reference teaches a number of different single chain antibody (SCA) fusion protein yeast expression vectors and yeast transformed with these vectors. The vectors comprise nucleotides encoding V_L and V_H subunits connected by linker sequences (page 2, lines 9-12, page 8, lines 6-11, and page 9, lines 12-20). The source of the nucleotides can be human or mouse (figures 7 and 8) and the V_L and V_H subunits may be encoded in either order from 5' to 3' (page 19, lines 9-27). The preferred peptide linker should be from 2 to about 50 or 18 to about 30 residues (page 21, lines 23-24 and page 22, lines 17-18). At least 18 different expression vectors are taught that comprise sequences in the two subunits that vary independently of one another (page 29, line 13 – page 30, line 22, page 67, lines 15-17, and page 76, claim 1.). The reference teaches that other proteins may also be modified including cell adhesion proteins, IgA, IgG, IgD, IgE, IgM, enzymes, cytokines, and growth factors (page 30, line 26 - page 31, line 14). The yeast expression vector includes the yeast 2μ circle (page 35, line 4) and is transformed into yeast (page 36, lines 8-10).

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use the linkers of Filupa et al. with the expression libraries of Hoeffler et al. According to Filupa et al. page 22, lines 15-19, "linkers having 18-30 residues are most preferred for SCA (single chain antibody) polypeptides in the monovalent conformation." Similarly, the same reference states "The preferred length of the peptide linker should be from 2 to about 50 amino acids. In each particular case, the preferred length will depend upon the nature of the

polypeptides to be linked and the desired activity..." One would have had expectation for success because linkers as disclosed in the references had already been used successfully.

The Gietz et al. reference teaches methods that allowed the authors to screen a yeast cell library of 5.2×10^7 transformants (page 266). The reference teaches that one may make libraries "of 1×10^6 independent clones **or more**." It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use the methods of Gietz et al. to optimize the method of Hoeffler et al. One would have been motivated to do this because doing so would increase the proportion of an antibody repertoire that could be screened. One would have had reasonable expectation for success because Gietz et al. had already produced large libraries in yeast for a 2-hybrid screen.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas Prasthofer** at telephone number (703) 308-4548. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

12. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

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13. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.



DR. JYOTHSNA VENKAT PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Thomas Prastrofer, Ph.D.

September 14, 2001